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DISTRIBUTION AND PREDICTORS OF HAEMOPHILIA-RELATED NON-DRUG DIRECT MEDICAL COST IN THE UNITED KINGDOM: ANALYSIS OF DATA FROM THE CHESS I AND CHESS II BURDEN OF ILLNESS STUDIES

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INTRODUCTION

- Haemophilia A and B are inherited bleeding disorders characterised by the deficiency or dysfunction of coagulation protein factors VIII or IX. Haemophilia is classified depending on the endogenous level of FVIII or FIX in the patient's bloodstream relative to normal levels, and can be mild (>5%-40%), moderate (1-5%) or severe (<1%).[1]
- Haemophilia is typically treated by means of replacement factor therapy to replenish the missing clotting factor, either prophylactically, to control and prevent bleeding or on-demand, to treat a bleeding event at the time of occurrence. [2,3]
- In the absence of effective treatment, haemophilia patients may experience severe and repeated bleeding episodes with their frequency increasing with condition severity. Bleeding most commonly occurs in the joints, soft tissue and muscles, causing short-term symptoms (reduced range of movement and/or pain) and long-term complications (chronic joint pain and/or haemophilic arthropathy). [4]
- Haemophilia poses a significant burden on patients and on the health-care system and a large body of literature examining the large burden of drug costs on the healthcare system exists.[5,6] However, remaining non-drug direct medical cost (DMC) provides a useful insight into the healthcare system burden and requirement relating to the management of haemophilia in addition to factor treatment. This is often overlooked but may be substantial and needs to be examined in light of the rapidly changing haemophilia treatment landscape.
- However, limited evidence is available on UK-specific haemophilia-related non-drug DMC and clinical outcomes or patient characteristics that may be driving it.

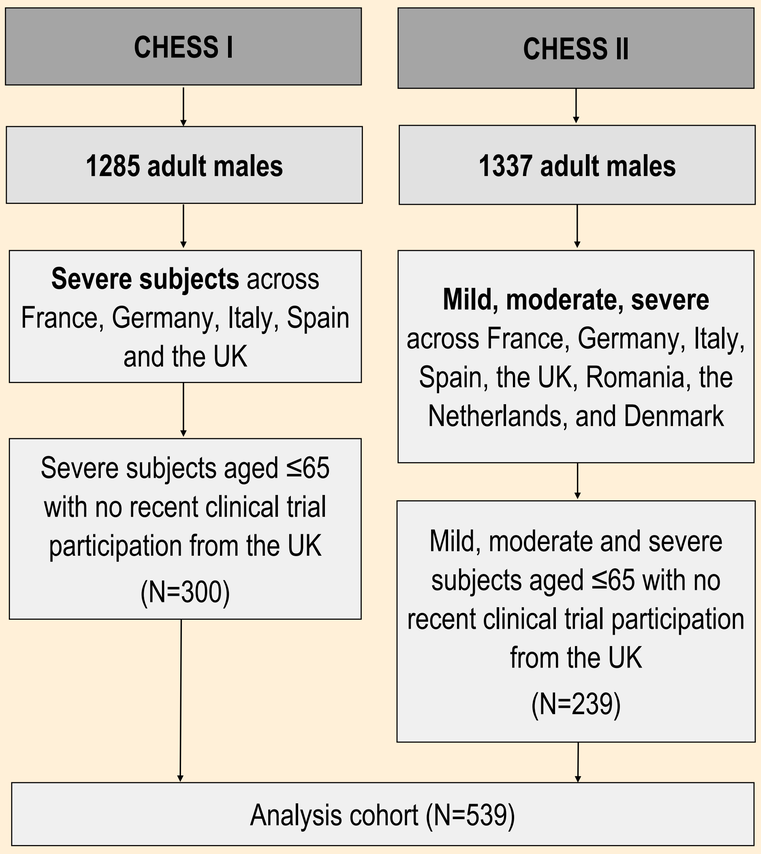
AIM

- This analysis aimed to assess the predictors of non-drug DMC, and quantify the relationship that clinical outcomes and patient characteristics have with aggregate non-drug DMC in subjects in the UK aged ≤65 years, using data from the 'Cost of Haemophilia in Europe: a Socioeconomic Survey' (CHESS) I and II retrospective burden-of-illness studies.[7]

METHODS

- UK data from the CHESS I/II cross-sectional burden-of-illness studies were analysed (Figure 1).
- Per-patient haemophilia-related annual DMC was quantified using physician-reported outcomes obtained from medical records of adult males aged ≤65 years with a formal diagnosis of inherited haemophilia A or B, and no recent clinical trial participation (Figure 1).
- Non-drug DMC cost components were calculated using publicly available unit cost data for the UK and comprised haematologist and nurse consultation visits, hospitalisations, surgical procedures and haemophilia-related specialist consultations/examinations.
- Patient characteristics and clinical outcomes were abstracted from the medical charts, including haemophilia type and baseline severity, inhibitor status, annual bleeding rate (ABR), number of problem joints (PJ; chronically damaged joints), treatment regimen and concomitant conditions information (grouped into 'blood-borne viruses' and 'other comorbidities').
- Patients with recent participation in a clinical trial or older than 65 were excluded. Treatment (Factor / non-factor replacement therapies) costs were excluded from the calculation of the non-drug DMC used in the statistical analysis. Non-drug DMC was assessed in the statistical analysis; however, total DMC was reported descriptively.

Figure 1. CHESS I and CHESS II studies



- A generalised linear model was employed to model non-drug DMC, quantifying the average marginal effect (AME) at the mean, controlling for patient characteristics and clinical outcomes.
- The Gamma error family was employed with a log link, due to the distribution of the outcome of interest. The inclusion of control variables was based on the univariable relationships between the parameters of interest as well as on the aim of building a clinically relevant and parsimonious model.
- Descriptive statistics are presented as mean (standard deviation (SD)) or N (%).

RESULTS

- Of 539 patients meeting the inclusion criteria, 396 (73.47%) and 143 (26.53%) patients had haemophilia A and B, respectively with a mean age of 32.4 (12.5) years (Table 1).
- Mean ABR was 3.2 (4.3); 377 (69.9%), 60 (11.1%), and 25 (4.6%) were reported to have experienced 1-5, 6-10, and 11+ bleeding events respectively. Over 40% of patients had at least 1 PJ, with 94 (17%) reporting two or more PJs (Table 1).
- The majority of the patients received prophylactic treatment (n=299; 55.5%]) with 223 (41.4%) receiving on-demand treatment and only 17 (3.2%) not receiving any treatment in the preceding 12 months (Table 1).
- The mean (SD) per-patient haemophilia-related DMC was £162,985 (£180,729) including drug costs. Non-drug DMC was £3,296 (£6,072) overall and £3,429 (£6,467) and £2,927 (£4,812) for haemophilia A and B, respectively (Table 1).
- While age was not a significant predictor of non-drug DMC, several other covariates were statistically significant determinants, including: haemophilia subtype, PJ number, ABR, treatment regimen and 'other' comorbidities (Table 2).
- Among the significant predictors, PJ number and ABR were associated with the largest AME in terms of magnitude (Table 2).
- Non-drug DMC increased by £1,690, £3,431, and £5,605 for patients with an ABR of 1-5 (n=377; 70%), 6-10 (n=70 ;11%) and ≥11 (n=25; 5%), respectively (Table 2).
- Each additional PJ represented an increase in non-drug DMC of £1,718, while, overall, presence of joint damage (≥1PJ) was associated with a mean (SD) increase of £2,833 (£1,683) (Table 2).

Table 1. Demographics and Baseline Characteristics of Patients (by Haemophilia type)

Patient Characteristics	Haemophilia A (N=396)	Haemophilia B (N=143)	Total (N=539)
Age; mean (SD) years	32.4 (12.3)	32.4 (13.0)	32.4 (12.5)
Presence of Inhibitors; n (%)			
Yes	11 (2.8%)	2 (1.4%)	13 (2.4%)
Blood-borne viruses[a]; n (%)			
Yes	31 (7.8%)	14 (9.8%)	45 (8.3%)
Other comorbidities; n (%)			
Yes	110 (27.78%)	38 (26.57%)	148 (27.5%)
Problem Joints[b]; n (%)			
0	224 (56.6%)	87 (60.8%)	311 (57.7%)
1	98 (24.7%)	36 (25.2%)	134 (24.9%)
2+	74 (18.7%)	20 (14.0%)	94 (17.4%)
Annual bleed rate[c]; mean (SD)	3.1 (3.8)	3.8 (5.3)	3.2 (4.3)
Annual bleed rate; n (%)			
0	58 (14.6%)	19 (13.3%)	77 (14.3%)
1-5	281 (71.0%)	96 (67.1%)	377 (69.9%)
6-10	41 (10.4%)	19 (13.3%)	60 (11.1%)
11+	16 (4.0%)	9 (6.3%)	25 (4.6%)
Treatment regimen; n (%)			
No treatment	14 (3.5%)	3 (2.1%)	17 (3.2%)
On-demand	180 (45.5%)	43 (30.1%)	223 (41.4%)
Prophylaxis	202 (51.0%)	97 (67.8%)	299 (55.5%)
Non-drug DMC; (£) mean (SD)	3,429 (6,467)	2928 (4,812)	3,296 (6,072)

Abbreviations: BMI, Body mass index; SD, standard deviation; DMC, direct medical cost [a]Comprised of hepatitis B virus, hepatitis C virus, and HIV (human immunodeficiency virus);[b]Joints exhibiting symptoms of chronic damage, including chronic synovitis, haemophilic arthropathy, limited motion, and/or recurrent bleeding;[c] Number of bleeding events the patient has had in the 12 months up to time of study capture.

Table 2. Predictors of haemophilia-related non-drug direct medical cost

Predictor	Incremental Cost vs Reference Value	95% CI	P value
Age	£10.86	(-19.33, 41.04)	0.481
Number of PJs	£1718	(1103, 2333)	<0.001
Annual bleed rate, ('0' reference)			
1 to 5	£1,690	(1,139, 2,241)	<0.001
6 to 10	£3,431	(1,887, 4,976)	<0.001
11+	£5,604	(2,311, 8,897)	0.001
Treatment regimen, ('No treatment' reference)			
On-demand	£1,412	(173, 2,651)	0.025
Prophylaxis	£1,691	(462, 2,920)	0.007
Haemophilia sub-type, ('A' reference)	£-923	(-1661, -185)	0.014
Inhibitors (current inhibitor present)	£3,927	(-716, 8,570)	0.097
Comorbidities (Present)			
Blood-borne viruses	£-795	(-1,988, 397)	0.191
Other comorbidities	£1,193	(307, 2,080)	0.008

Abbreviations: CI, confidence interval; vs, versus

CONCLUSIONS

- Haemophilia is associated with substantial DMC in the UK. Non-drug DMC is related to key clinical outcomes, with frequency of bleeding events and chronic joint damage demonstrating the largest effect.
- Improved condition management and treatment approaches aimed at reducing ABR and preventing PJs could play a substantial role in reducing non-drug DMC. As novel treatments affording steady state protection become available, the focus of condition management may start to shift to longer-term chronic complications.
- The findings of this analysis provide an initial contribution to the literature concerning the determinants of non-drug DMC associated with haemophilia in the UK. Additional research on the specific impact of the number of bleeding events and chronic joint damage, as well as other haemophilia-related complications on DMC is needed, to refine and fortify the evidence base informing the economic evaluation of future haemophilia treatments in the UK.

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